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ENDOCRINE GLANDS

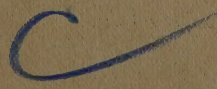
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CONTROL OF BODY TEMPERATURE

BY

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From the Laboratories of Physiology of the Harvard Medical School

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STUDIES ON THE CONDITIONS OF ACTIVITY IN ENDOCRINE GLANDS

XXI. THE RÔLE OF ADRENAL SECRETION IN THE CHEMICAL CONTROL OF BODY TEMPERATURE¹

W. B. CANNON, A. QUERIDO,² S. W. BRITTON³ AND E. M. BRIGHT

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Erection of hairs, ruffling of feathers, constriction of peripheral vessels, increase of blood sugar (Embden, Lüthje and Liefmann, 1907; Freund and Marchand, 1913) are well-known phenomena occurring when warm-blooded animals are exposed to cold. They are reactions which have been interpreted as useful in protecting the organism against a reduction of the body temperature; for the raised hair and feathers enmesh a thicker layer of air around the body, the constricted surface vessels lessen the heat loss, and the extra blood sugar provides a readily combustible material for increase of heat production. Erect hairs, pallor and a higher glycemic percentage are characteristic also of emotional excitement—i.e., in the disturbances produced by cold, and by strong emotion as well, there are signs that the sympathetic division of the autonomic system is in action. The question naturally arises, Is secretion from the adrenal medulla, which is admitted to be under sympathetic control, augmented when cold causes a discharge of sympathetic impulses? The answer to this question has interesting physiological bearings, for, as shown by earlier studies in these Laboratories by Aub, Bright and Forman (1922), and by McIver and Bright (1924), absence of medulliadrenal secretion lessens the rate of metabolism, and increase of that secretion accelerates the oxidative processes. If the adrenal medulla is excited to extra activity by cold the extra adrenin discharged would effect a faster burning in the body just when there would be need for it.

Cramer (1919) has published figures showing the appearance of adrenal glands taken from mice which had been exposed to extreme or to moderate cold. After exposure to extreme cold the medullary cells lose their outlines

¹ A report of our first observations was made to the National Academy of Sciences in April, 1924 (see Proc. Natl. Acad., 1924, x, 245).

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and the "adrenalin granules," which normally fill the cells as an evenly distributed fine dust, are no longer visible. After exposure to more moderate cold the appearance may be indistinguishable from the resting gland. Vincent (1925) has reported similar observations on white rats; considerable reduction of the temperature of the surroundings caused a lessening of the chromaphil reaction if the animal's temperature became lowered. In 1921 Fujii announced that the content of chromaphil substance in the adrenal medulla was reduced in rabbits which were fastened to an animal board, but that the reduction was very slight if the rabbits were protected against loss of body temperature, and did not occur at all if the splanchnic nerves had previously been cut. From these results the inference might be drawn that by rousing splanchnic impulses cold induces so great a discharge of adrenin that there is actually a depletion of the stored material in the gland. But as Trendelenburg (1923) has noted, this observation should be interpreted cautiously, for in the cooled animal the production of adrenin may be retarded or diminished. This is a comment which applies also to Cramer's and to Vincent's results.

More direct evidence of increased adrenal secretion in consequence of heat loss was furnished by Hartman, McCordock and Loder (1923) and by Hartman and Hartman (1923). They observed that when cats with a completely denervated iris are dipped in cold water, or when they are dipped in warm water and while wet are placed in a cold room or exposed to a current of cool air, the pupil is dilated if the adrenal glands are present, but not if the glands have been removed or if one has been removed and the other denervated. Their method required holding the cats firmly during the immersion, and they mention struggling by the animal as an accompaniment of the procedure. They conclude, however, that in most instances excitement did not appear to be an important factor in the reaction to cold, for no change in the pupil or only a slight change occurred when the animals were put into water at body temperature. The increased medulliadrenal secretion, which they inferred from the dilated pupil, they attributed to peripheral stimulation rather than to a general fall of body temperature.

The method used by Hartman and his associates has been severely criticized by Stewart and Rogoff (1923). They state, "A progressive dilatation of the pupil as an experiment goes on is a very common thing indeed. This has been abundantly proved in our own work to be no indication of increasing epinephrin output." The casual reader might suppose from this statement that Stewart and Rogoff had used the denervated iris. The preparation which they have employed, however, was the iris deprived only of its *sympathetic* innervation. In 1915 and again in 1919 it was pointed out that calling such a preparation a "denervated eye" was unwarranted, and that the dilatation of the pupil under the

circumstances might be complicated, e.g., it could be accounted for by central inhibition of the still active constrictor muscles of the iris, as well as by increased secretion of adrenin (Cannon, 1919). So long as two factors may be producing the same effect a sound inference is impossible until the part played by each is clearly distinguished and evaluated. Stewart and Rogoff (1920) responded that they were quite well "aware that the oculomotor nerve supplies the eye," and that they had used the expression "denervated eye" for convenience. Hartman, however, was not using a similar expression for convenience. He was doing what he said, i.e., employing the *completely* denervated iris, after removing both the ciliary and the superior cervical ganglia. Since Stewart and Rogoff have not observed the denervated iris in any exact sense, their experience has little pertinence. When they state (1923) "in our opinion" the method is quite inadequate, and "we do not think" any of Hartman's statements that cold increases the adrenin output could be proved true by his method, it is well to recognize how slight is the basis for their judgments. And when they declare that conclusions based on the denervated iris and the "denervated heart, without quantitative estimations of the output, have no real foundation," it is well to recall that the denervated heart has been used for quantitative assays of the adrenin output (Cannon and Rapport, 1921; Anrep and Daly, 1925) and that these assays showed, contrary to the assertions of Stewart and Rogoff, that the output is greatly increased by reflex stimulation and asphyxia.

Ever since the observations of Aub, Bright and Forman we have planned experiments to test the important question of a possible rôle of increased medulliadrenal secretion in the chemical control of body temperature. The results obtained by Hartman and his co-workers marked definite progress in answering that question. Because those results have been doubted, however, and also because we desired to eliminate or to minimize quite certainly the disturbing factors of emotion and struggle in the reaction to cold, we have investigated the reaction by other methods.

THE INCREASED OUTPUT OF ADRENIN DUE TO COLD. The indicator for increased medulliadrenal secretion which we have employed is the denervated heart in unanesthetized animals. In a previous paper of this series (Cannon, Lewis and Britton, 1926) the method of isolating the heart from the central nervous system and still leaving one vagus nerve to care for the alimentary tract has been described. The animals (cats) thus prepared live quite normally in the quiet conditions of the laboratory. The heart is influenced only by the effective agents brought to it in the blood stream, and by temperature changes. It is highly sensitive to circulating adrenin; Cannon and Rapport (1921) noted that intravenous injection of adrenalin, 0.00068 mgm. per kilo per minute, increased the pulse in the cat as much as 34 beats per minute; and Anrep and Daly

(1925) have reported that the isolated heart of the cat is sensitive to adrenalin in the solution 1:1,400,000,000. When one adrenal gland has been removed and the other thoroughly denervated, and the hepatic nerves have been severed, the denervated heart no longer accelerates to a noteworthy degree under conditions which normally would excite medullary adrenal secretion (Cannon, Lewis and Britton, 1926). It is, therefore, a reliable indicator.

For the purpose of the present enquiry the denervated heart has advantages over other denervated organs. First, it renders the conditions of the experiment unfavorable to the expected result; for the natural influence of cooling is to decrease the rate of the isolated heart (Knowlton and Starling, 1912), and if cooling evokes a greater output of adrenin and thereby a cardiac acceleration, the acceleration is induced in spite of an influence directly opposed to its occurrence. Again, the denervated heart has advantages in that the changes of rate whereby it manifests its response can readily be determined by auscultation or palpation, or by combination of the two, or can be easily registered by a mechanical device or in an electrocardiogram.

Method. We employed several different methods of exposing animals to cold. Our first method was that of holding the animal, warm and comfortable, in the lap near a window, and after the heart rate had been counted or registered, opening the window to let in cold air. In some respects this method was quite satisfactory—excitement and motion were eliminated because the surroundings were familiar to the animal; and the observer could listen to and record the heart beat, watch and feel for muscular quivering, and note the animal's temperature, without inconvenience. The defect of the method lay in its limitation to periods of cold weather.

We also used a refrigerating room, large enough to receive two observers, that was kept at about 5°. The disadvantages of this method of test were *a*, strangeness of surroundings which, according to our experience, may be accompanied by movement (exploration), and this by a heart beat somewhat more rapid than in the quiet state; *b*, inconvenience for continued observation, and *c*, remoteness from recording apparatus. Its great advantage, when the animal remained quiet, was complete freedom from disturbance due to excitement or struggle. Though the pulse could not be mechanically recorded, it could be easily counted by means of a stethoscope.

The most generally serviceable method which we employed was that of introducing into the stomach a known amount of cold water. Various observers have studied the influence of ingested water on metabolism. Laschtschenko (1898) observed no noteworthy increase in carbon-dioxide production when the temperature of the water was 37°. Speck (1892)

concluded from two tests on himself that metabolism is not influenced by drinking large amounts of water (1250 to 1500 cc.) but he did not report its temperature. Benedict and Carpenter (1918) performed five calorimeter experiments on subjects who, during the period of observation, drank between 1584 and 3985 cc. of water at approximately room temperature, and six respiration experiments on subjects who drank between 200 and 325 cc. of water at temperatures ranging from 50.5° to 58°, and, in one case, 500 cc. at 11°. In all the experiments except two the heat increment over the basal value did not exceed 4 per cent; in the two the increments were 15 and 16 per cent. A subject in one of these two tests (J. J. C., "an unsatisfactory subject in many ways") whose metabolism increased 15 per cent when he drank 1800 cc. at 21°, had an increase of only 3 per cent when in another test he drank 1547 cc. at 21°. It seems probable, therefore, that disturbing factors entered into these two anomalous cases. However that may have been Benedict and Carpenter concluded that when not more than 500 cc. of water are taken, whether at 22° or 55°, no significant increase of basal metabolism results. The general testimony of observers of human conditions is that drinking moderate amounts of water at intervals during a test, and with temperatures not far removed from that of the body, does not influence the metabolic rate to a noteworthy degree.

The most definite evidence that cold water increases basal metabolism is that presented by Lusk (1915). He found that when glucose was given in cold water (16.5° to 18°), or when cold water was given alone, there was a discrepancy between the results obtained by direct and indirect calorimetry—a discrepancy which disappeared when water at body temperature was used. That the discrepancy was chiefly due to extra heat production and not to passage of heat from the animal to the cold water and therefore not to the calorimeter is indicated by close correspondence of the average figures for the caloric output as determined by direct calorimetry whether the water was cold (75.19 calories in three hours) or warm (76.39 calories), and the lack of such correspondence when the determination was indirect (80.33 calories with cold water, and 75.92 with warm water).

In none of the researches cited above was cold water employed in order to study systematically the responses and adjustments which the organism might employ in order to prevent the lowering of body temperature. In our experiments we have used cold water at a fairly uniform low temperature; it was introduced into the stomach quickly by stomach tube or more commonly, in man, by rapid drinking. In the tests made on cats the animals were placed in a box provided with a sliding cover which had an opening at one end through which the head emerged. A catheter was readily introduced by passing it through a hole in a piece

of wood held between the animal's teeth by pressure with the hand on the upper and lower jaws. When in the tests on man the stomach tube was used it was gently pushed down the esophagus to the accompaniment of swallowing motions. Doubtless there was a disturbance due to the introduction of the tube, in both cat and man, but as control observations, to be reported later, have shown, it soon subsided. In the human experiments in which cold water was drunk it was siphoned through a short tube from a beaker. Thus the position of the subject was not changed and large muscles were not brought into action. Crushed ice was given by spoon in some cases, for the extra calories required to melt the ice (80 calories per gram) are added to those required to bring the melted ice to body temperature, and thereby the same task can be set the organism in smaller bulk than if water alone is employed. This idea was suggested to us by Boothby. The use of cold water has several advantages: *a*, it can be given anywhere and consequently strange surroundings are avoided; *b*, it permits direct observation of effects on body temperature, heart rate and shivering, and also ready registration of changes by mechanical or electrical methods; *c*, it is easily available at any time, and *d*, it is satisfactorily quantitative. The last advantage is most important. The weight of the animal and its rectal temperature and specific heat, the volume of the introduced water and its temperature and specific heat, can all be known. By assuming that the circulation makes the introduction of cold water into the stomach and intestines equivalent to mixing it with the body fluids (i.e., equivalent to adding the same amount of cold water to a bulk of fluid having the temperature, volume and specific heat of the organism), it is possible to calculate how much a certain amount of cold water would lower the body temperature, if no extra heat were produced or conserved. For example, if in the case described in the protocol on page 480 we should assume that the circulating blood brings heat from all parts of the body to the splanchnic region where the cold water lies exposed to an extensive capillary area, if we should assume further that the water (120 cc., at 1° , and with specific heat 1) produces only physical effects in the body of the animal (2400 grams, at 39.6° , and with specific heat 0.83), and that additional loss of the body heat to the surroundings may be neglected, the resultant temperature, after complete mixing, would be 37.3° . In other words, the temperature of the animal would fall 2.3° . The fall within five minutes was 1.8° , but after twenty minutes it was only 1.2° . Heat producing or heat conserving factors, or both, of a physiological character, must have been set at work, therefore, not only to prevent the temperature from dropping but also to restore it. The heat-producing task confronting the organism, if normal temperature is to be maintained, can thus be fairly accurately known. This may be called the "heat tax," or "heat levy," or "heat

debit," or "heat liability," or "heat debt" of the organism. We shall use the last mentioned term.⁴

A number of conditions may influence the reaction of the body to the cold water that is introduced. If the water should remain as a mass in the stomach, heat would pass into it more slowly than if the water should be pressed out from the stomach and spread along the small intestine so as to present an extensive surface. Quite possibly the rate of the gastric discharge of water into the intestine may vary somewhat in different animals, but as a rule water is quickly moved onward (see Cannon, 1911). There is little reason for supposing that an important factor lies there. Doubtless, also, the adrenin set free during the disturbance caused by passing the stomach tube may play a part in meeting the heat debt—a small part, probably, because the disturbance is brief. Again, the external temperature is undoubtedly important as affecting the influence of the "heat debt." If the room air is 19° the organism is losing more heat to the surroundings than if the room air is 25°. A given heat debt produces greater physiological effects in the former than in the latter case (see table 7). In the winter it is possible to minimize this factor by keeping the room air about 20°. Finally, the initial temperature of the water is significant; thus, though 100 cc. of water at 1° present the same heat debt as 132 cc. at 10°, when the body temperature is 38°, yet in the body the heat passes so much more rapidly into the colder than into the warmer water that these two equal "debts" would have different physiological effects (see fig. 3). In order to lessen the influence of the initial temperature factor we have generally used water between 0° and 1°. With this factor and the external temperature fairly constant, it is clear that the heat debt can be varied at will, and adjusted nicely to the weight or to the estimated surface of the animal and to the purposes of the experiment.

We did not make numerous tests on the effect of cold because while engaged in this research we were using the same animals to study the influence of emotion (see Cannon and Britton, 1926) and were so well acquainted with them and so confident concerning the significance and reliability of their responses that relatively few experiments sufficed to

⁴ In the preliminary report (Proc. Natl. Acad., 1924, x, 245) on the experiments here described in detail the term "heat liability" was employed. Since then (Proc. Roy. Soc., 1924, xevi, 442) Hill, Long and Lupton have introduced the conception that the organism by developing lactic acid beyond the oxygen requirement incurs an "oxygen debt," which must later be met by increased oxygen supply until normal conditions prevail again. The condition is similar to that which is present when cold water is introduced into the body. Since the term "*debt*" is briefer than "*liability*" and has already become established in physiological literature, we are using it instead of "*liability*."

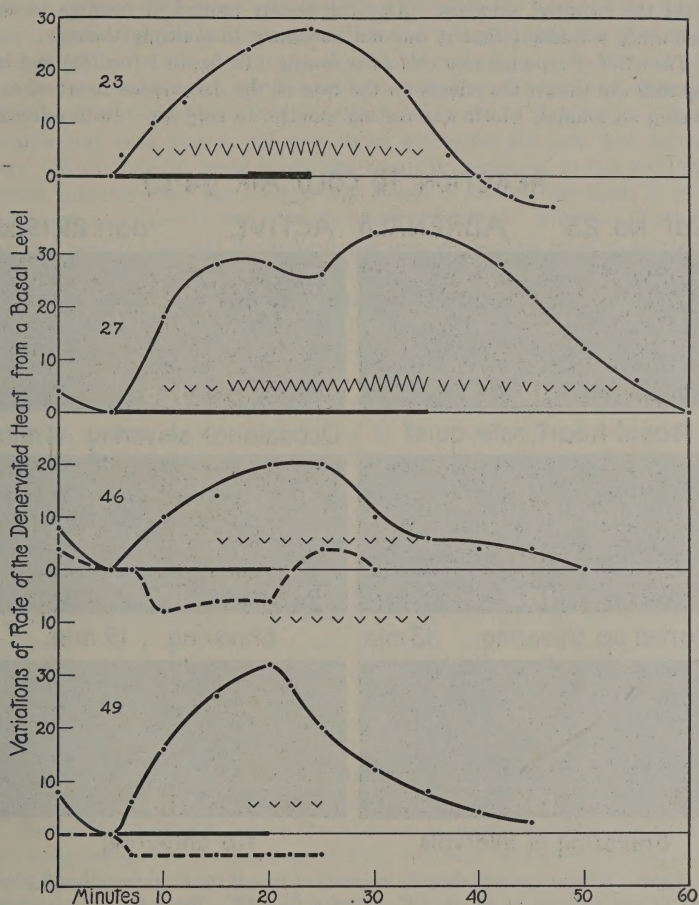


Fig. 1. Increases of rate of the denervated heart above a basal level when animals with adrenals intact (nos. 23, 27, 46 and 49) were exposed to cold air. The period of exposure is denoted by a thickening of the base line; the double thickening in the case of no. 23 marks the time of a cold draught through an open door. Shivering is indicated by separate *v*'s when it was intermittent, and by connected *v*'s when it was continuous. The size of the *v*'s marks roughly the intensity. The dash-lines in cases 46 and 49 show the changes of heart rate under similar conditions of exposure after exclusion of medulliadrenal secretion.

yield the required evidence. Also the results proved at once to be so uniformly consistent that it was not necessary to multiply them.

The effect of exposure to a cold environment. In figure 1 (no. 23) and in figure 2 are shown the effects on the rate of the denervated heart of exposing an animal, which was resting quietly, to cold air. Both adrenal

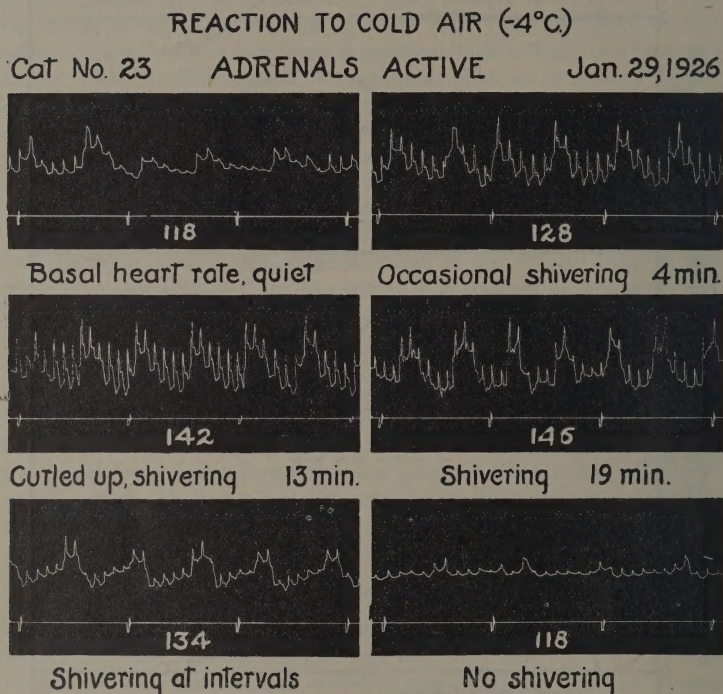


Fig. 2. Original records showing increases of rate of the denervated heart when cat 23 was exposed to air at -4° , January 29, 1926. Below the records taken while the window was open are written figures telling the time after the opening. Eight minutes after closing the window the rate had fallen from 146 to 134, and twelve minutes later to 118 (the basal). Time in five-second intervals.

glands were intact. The date was January 29, 1926. The room temperature was 16° , the outdoor temperature was -4° . The assistant sat on a table next a closed window, with the cat on a board in his lap. The tube of the recording apparatus reached to the kymograph. The basal rate was registered at 118 beats per minute. Four minutes after the win-

dow was opened the heart rate had risen 10 beats per minute. In thirteen minutes the rate had increased 24 beats. At that time the door was opened so that a strong draught of cold air rushed by. At the end of the next six minutes (i.e., 19 minutes from the start) the rate had reached 146 beats per minute—i.e., 28 above the basal, a rise of 24 per cent. The window was then closed. Nine minutes thereafter the rate had fallen from 146 to 134—16 beats above the basal; it continued to fall until in sixteen minutes after the window was closed it reached the basal (118). Seven minutes later it was 6 beats below that level. We would stress the fact that the animal throughout the test was resting quietly, so that the reaction was not complicated by stimulation of the adrenal medulla by excitement or gross bodily movements. The back was hunched up, with the feet nestled underneath the body, and the tail held close at the side. Four minutes after the window was opened the hairs were standing and continued thus until four minutes after closing the window when the animal was covered. Shivering occurred after the first four minutes of exposure; at first it was slight, limited to the shoulders, and occasional. As time passed, and coincident with the increasing heart rate, the shivering became more general, more vigorous, and was marked with each inspiration. Twelve minutes after the window was closed there was still occasional very slight shivering. This was three minutes before the heart beat returned to the basal rate.

On February 11 the adrenals of this cat were inactivated. On February 23, when the animal was again energetic, and the out-door temperature was again low (-6°), the test was repeated, with the exception that after twelve minutes near the opened window the cat was placed in a small wire cage and set outside on the ledge for ten minutes. The visible reactions of the animal to the cold were similar to those seen on January 29. The heart rate, however, instead of increasing 28 beats per minute, rose only 6 beats, and later fell 4 beats below the basal before restoration to its former condition. The only difference to account for this change in the cardiac response lay in the absence of medulliadrenal secretion. The completeness of the removal of that influence on the heart was repeatedly proved in this case by absence of the fast rate after struggle (see Cannon and Britton, 1923, table 3).

The observations on cats 27, 46 and 49 (fig. 1) were made in a refrigerating room. The rate of the heart was not mechanically recorded, but was counted by the aid of a stethoscope and stop watch. As indicated by the heavy portion of the basal line in the graph for no. 27 (fig. 1), the animal was exposed to cold for 30 minutes. During this time it rested on a metal tray supported on the observer's lap. During the first five minutes there was no shivering; the hair was slightly ruffled; the pulse rose 18 beats. During the second five-minute period the fur became very

TABLE 1

Increases of rate of the denervated heart after introducing cold water into stomach. The italicized figures were recorded in control experiments, either with warm water while the adrenals were intact or with cold water after adrenal inactivation

CAT NUMBER, DATE	CAT WEIGHT	ROOM TEMPERATURE	AMOUNT WATER GIVEN	TEMPERATURE OF WATER	HEAT DEBT* CAL. PER KILO	BASAL BEFORE WATER GIVEN	HEART RATE IN BEATS PER MINUTE													
							Increases over basal after water given													
							1-2 m.	5 m.	10 m.	15 m.	20 m.	25 m.	30 m.	35 m.	40 m.	45 m.	50 m.	55 m.	60 m.	
(26) 3/16/26 3/20/26 3/22/26 3/22/26§ 4/1/26	kgm.	°C.	cc.	°C.																
	2.8	24.0	200	10	2000	120	132	64	20	12	8	6	0†							
	2.4	24.5	130	1	2000	92	116	50	24	24	20	16	8	4	6					
	2.4	26.5	130	34	220	90	124‡	70	22	8	2									
	2.4	26.5				90	76	26	6											
(27) 3/13/26 3/17/26 3/22/26 4/10/26	2.5	21.0	135	10	1510	104	-12	12	-12	-16	-22	-14	-18	-16	-16	-14	-16	-16	-8	-8
	3.3		236	10	2000	130	56	44	32	20	14	12	6	2	0					
	3.3	24.3	162	1	1820	120	44	36	32	34	26	30	20	20	12	8	4	4	0	0
	3.2	26.5	162	33	250	124	36	8	0											
	2.4	24.0	130	1	2000	104	8	2	0											
(33) 4/16/26 4/28/26 4/29/26 5/5/26	2.4	20.5	120	1	1850	118	42	34	30	22	26	26	26	18	22	22	18	16	12	12
	2.7	23.0	146	1	2000	120	32	38	28	20	16	12	10	14	10	8	8	0	0	0
	2.6	22.0	146	31	390	132	36	8	4	0										
	2.2	25.6	116	1	1950	122	10	6	2											
(46) 6/23/26 7/23/26	2.9	23.7	162	1	2070	126	22	18	18	14	12	6	2	2	0					
	2.9	22.5	162	1	2070	120	-8	-8	-8	-12	-10	-8	-8	-6	-4	0				

rough, there were occasional slight tremors, and the pulse rate increased 10 beats more, i.e., to 28. Then, as shown in the graph, shivering became general and continuous, though moderate, with no marked change in the cardiac contractions, until ten minutes had passed. By this time the hair was bristling on all exposed parts of the body. Thereupon the shivering became gradually more and more vigorous, and the animal became restless. The heart rate rose to 34 beats above the basal figure, a rise of 27 per cent. At the first observation made after removing the animal from the cold room the rate had fallen 6 beats; it continued to fall gradually until at the end of twenty-five minutes in warm surroundings it reached the basal again. No control tests for the effects of cold were made on this animal after adrenal inactivation; but the repeated failure of the heart to accelerate in the supreme test of struggle, after exclusion of medulliadrenal influences (see Cannon and Britton, 1926, table 3), proved that the acceleration in the cold room resulted from increased output of adrenin.

The graph for no. 46, figure 1, is similar to that for no. 27, and is self-explanatory. The percentage increase of heart rate was 18. When, after the right adrenal gland had been excised and the left denervated, the animal was again kept in the cold room fifteen minutes, as before, the heart rate, instead of rising, fell 8 beats per minute. It continued low until the animal was brought, shivering, into a warm atmosphere. There followed a quick rise to 4 beats above and then a subsidence to the basal.

The protocol of observations on no. 49 (fig. 1) in a cold-room experiment is given below. Taking the rectal temperature of the cat would be so disturbing that it would vitiate the experiment. Instead, the temperature was taken by holding the thermometer enclosed in the inguinal fossa.

Cat 49. June 22, 1926. In hallway, temp. 23.5°. Inguinal temp. of cat 38.7°. 11:40, basal h. r. (heart rate), 104 beats per minute. 11:45, h. r. 96. 11:46, *in cold room* on metal tray; temp. room 5.5°. 11:47, h. r. 104. 11:50, cat huddled up, hairs rough on back; h. r. 112. 11:55, no shivering, slight restlessness (movement of feet), inguinal temp. 37.9°, h. r. 122. 11:58, slight tremors in shoulder region, associated with inspiration. 12:00, hairs erect, inguinal temp. 37.1°, h. r. 128 (an increase of 33 per cent). 12:02, *out of cold room*, in hall, temp. 23.5°, h. r. 124. 12:05, slight tremors occasionally with inspiration, hairs smooth, inguinal temp. 37.9°, h. r. 116. 12:10, very quiet on lap, cat curled up on cushion, no tremors, h. r. 108. 12:15, inguinal temp. 38.1°, h. r. 104. 12:20, curled up, very quiet on lap, h. r. 100. 12:25, same condition, h. r. 98.

On June 24, the adrenals were inactivated in this cat. Thereafter for ten days all tests (exposure to dog and struggle) failed to cause any marked increase of heart rate. And when (July 2) the animal was taken to the cold room for 15 minutes the heart, instead of accelerating, beat more slowly (see fig. 1).

The effect of introducing cold water. In observations on the denervated heart after introducing cold water into the stomach there was found a very rapid rate immediately or as soon as the beats could conveniently be counted (see table 1 and fig. 3). This acceleration is due to the disturbance of the animal on being confined to a box and having a catheter passed through the mouth and esophagus, for it occurs for a brief period after that procedure alone (see table 1, no. 26, March 22) and also after introducing warm water (see table 1, no. 33, April 29, and fig. 3, C). In about ten minutes the rate falls from the initial peak to a plateau, and after remaining there for a varying time it gradually returns to the former basal value (see fig. 3, B).

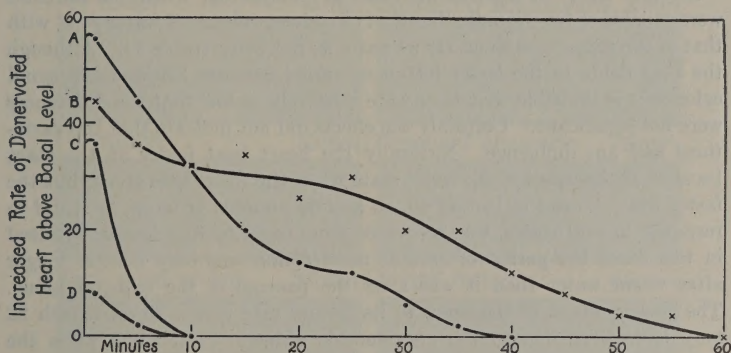


Fig. 3. Increases of rate of the denervated heart in cat 27, responding to heat debts produced by introducing water into the stomach under different conditions. A, B and C, with adrenals active. A, a heat debt of 2000 small calories when the water was given at 10° . B, a heat debt of 1820 calories, water at 1° . C, a heat debt of 250, water at 33° . D (with adrenals inactivated), a heat debt of 2000 calories water at 1° .

The results summarized in table 1 show the effects produced by heat debts between approximately 1500 and 2000 small calories per kilo when the temperature of the water was 10° (no. 26, March 16, and no. 27, March 13) and when the temperature was 1° or less (nos. 26, 27, 33 and 46). In the same animal the colder water had a more prolonged influence in speeding up the denervated heart than did the warmer water, though the heat debt was about the same (cf. fig. 3, A versus B). Comparison of the increments of heart rate after the establishment of the same heat debt, with the adrenal glands intact and after their inactivation, brings out a remarkable difference (cf. also B and D, fig. 3). Instead of an acceleration ranging between approximately 20 and 30 beats per minute in

the plateau region and representing (with the exception of no. 46, which on June 23 had a respiratory infection) increments varying between 23 and 28 per cent, that did not completely disappear for 40 or 60 minutes, when the adrenals were active, the acceleration, *after* the adrenals were excluded, either failed to occur (as in no. 26, April 1; and no. 46, July 2) or was slight even at the peak and usually had disappeared at the end of ten or fifteen minutes (see no. 27, April 10 (fig. 3, *D*); and no. 33, May 5).

The last five series of figures in table 1 were obtained by tests on cats with known adrenal inactivation (see Cannon, Lewis and Britton, 1926). No tests were made before the inactivation. The results closely correspond to those of the controls described in the preceding paragraph.

Another mode of control was that of comparing, when the adrenals were capable of functioning, the effect of a given volume of water at 1° with that of the same volume nearly as warm as the body (table 1). Although the heat debts in the latter instances varied between 220 and 390 small calories it is probable that they were relatively so low that the differences were not significant. Certainly the effects did not indicate that the variations had any influence. Naturally the heart beat faster at the start because of the upset of the quiet state when the water was given, but the faster beat, instead of lasting 40, 50 and 60 minutes or more, as it did in response to cold water, was recovered from in 10 or 15 minutes. Indeed in two cases the period of cardiac acceleration was only a little longer after warm water than it was after the passage of the catheter alone. The slower return of the heart to its former rate in no. 26 on March 22 may have been due to the considerable struggle in the box when the water was given.

Protocols presenting details of observations on cat 33 (see fig. 4) follow:

Cat 33, April 16, 1926. *Adrenals active*. Basal h. r. (heart rate), 118 beats per minute; inguinal temp. 39.6°, room temp. 20.5°. At 2:52 p.m., 120 cc. water at 1° (1850 cal. per kilo) given by stomach tube. At 2:56, h. r. 160, hairs standing. 2:57, h. r. 152, occasional shivering, inguinal temp. 37.8°. 3:02, h. r. 148, inguinal temp. 37.8°, fur rough. 3:07, h. r. 140, shivering more frequent. 3:12, h. r. 144, inguinal temp. 38.4°. 3:17, h. r. 144. 3:22, h. r. 144, shivering with inspiration, otherwise very quiet in lap, room temp. 20°. 3:27, h. r. 136, inguinal temp. 38.7°, occasional tremors. 3:32, h. r. 140, slight shivering. 3:38, h. r. 140, no shivering. 3:42, h. r. 136. 3:47, h. r. 134. 3:49, h. r. 132, very quiet in lap all this time. 3:52, h. r. 130.

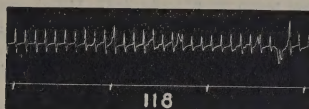
April 29, 1926. *Adrenals active*. Basal h. r., 10:42 a.m., 132 beats per minute. At 10:50, 146 cc. *warm* water (at 31°) by stomach tube, vigorous struggling while water given. 10:51, h. r. 168. 10:52, h. r. 160. 10:55, h. r. 140. 10:58, h. r. 134. 11:00, h. r. 136. 11:05, h. r. 132.

Fig. 4. Original records showing increases of rate of the denervated heart when cat 33 with active adrenals was given, April 16, 120 cc. of water at 1° (heat debt, 1850 small calories), and when, with adrenals inactivated, it was given, May 5, 116 cc. of water at 1° (heat debt, 1950 calories). Below each record are stated the prevailing conditions and the interval since the water was given. Time in 5 seconds.

CAT NO. 33

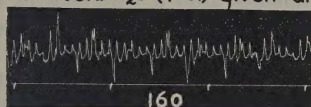
APRIL 16, 1926

ADRENALS



ACTIVE

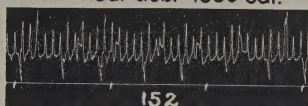
Basal heart rate, quiet on lap
Cold H₂O (1°C.) given at 0 min. Heat debt 1850 cal.



160

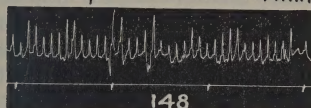
Fur rough

4 min.



152

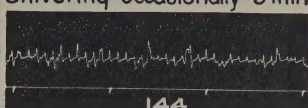
Shivering occasionally 5 min.



148

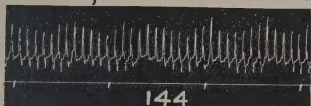
Fur rough

10 min.



144

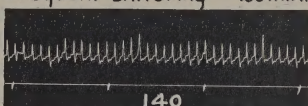
Frequent shivering 20 min.



144

Very quiet on lap

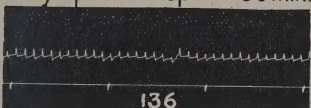
30 min.



140

Slight tremors

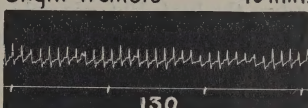
40 min.



136

No shivering

50 min.



130

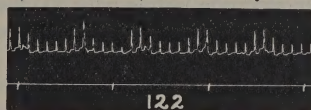
No shivering

60 min.

CAT NO. 33

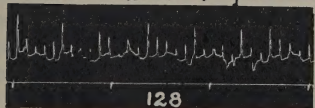
May 5, 1926

ADRENALS



INACTIVE

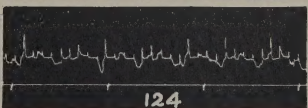
Basal heart rate, quiet on lap
Cold H₂O (1°C.) given at 0 min. Heat debt 1950 cal.



128

Slight shivering

5 min.



124

Frequent shivering

10 min.

Fig. 4

May 5, 1926. *Adrenals inactive*. 3:35 p.m., basal h. r., 122 beats per minute, inguinal temp. 39.5° , room temp. 25.6° . At 3:47, 116 cc. water at 1° (1950 cal. per kilo), given by tube. 3:48, h. r. 132. 3:52, h. r. 128, moderate shivering. 3:57, h. r. 124, frequent shivering, inguinal temp. 38.2° , very restless on lap. 4:02, inguinal temp. 37.2° , cat vomited large amount of watery fluid. 4:12, inguinal temp. 37.8° . 4:17, occasional slight shivering.

In the foregoing protocols note that on April 16 the inguinal temperature fell from 39.6° to 37.8° in five minutes after a heat debt of 1850 calories was established. Calorigenic agencies were at once invoked as shown by the faster pulse and by shivering. There was no further fall. During the next fifteen minutes the inguinal temperature rose to 38.4° . The room temperature near the cat was 20.5° to 20° . After the adrenals had been inactivated, a heat debt of 1950 calories caused a drop of the inguinal temperature from 39.5° to 38.2° in ten minutes, and to 37.2° in the next five minutes. The room temperature (25.6° as compared with 20.5° before) was unfavorable to this marked lowering of the temperature of the animal. The ejection of a considerable amount of the cold water saved the animal from a continuance of the heat loss. Since the maximal increase of the heart rate was only 10 beats, and ten minutes after the water was given the rate had returned to 124, only two beats above the basal (122), the experiment had proved a satisfactory control.

It is noteworthy that when the heat debt was 2000 calories and the room temperature was 23° (in no. 33, April 28) a more rapid recovery occurred than when the heat debt was only 1850 and the room temperature was 20.5 (April 16). This effect of warm surroundings was illustrated also in experiments on no. 41, which have not been reported above because in this case vagus connections were renewed before control experiments were performed. In no. 41, a heat debt of 2000 calories (water at 1°) caused cardiac acceleration, with a plateau at 48 beats above the basal, that lasted for 65 minutes when the room temperature was 19° ; the same heat debt caused an acceleration lasting only 30 minutes when the room temperature was 25° . Results of similar character were noted in human cases, to be described below.

Another condition which is doubtless important in affecting the degree of the cardiac response is the presence of shivering. In the above cases it differed in duration and intensity, as already noted (see fig. 1). It was usually most marked when the heart rate was most elevated. But it is not a necessary condition for the faster pulse—e.g., no. 26 on March 16 (table 1) met the heat debt of 2000 calories (water at 10°) with no shivering whatever. And regularly shivering does not occur at the beginning or near the end of the cardiac response (see especially nos. 46 and 49, fig. 1). In the cases reported above, however, the heat debt was paid not by the one process of increased discharge of adrenin, as indicated

solely by a more rapid heart beat, but also by muscular tremors. This muscular activity may be associated with an increased stimulation of the adrenal medulla (see Cannon and Britton, 1926), and in so far as a larger output of adrenin augments heat production in the body it may lessen the need for shivering. These points will be considered again.

All methods which we have used to threaten a fall of body temperature have evoked noteworthy acceleration of the denervated heart, so long as the adrenal glands were in their proper functional relations. When one of the glands was removed and the other denervated, exposure of the animal to cold surroundings and introduction of cold water into the stomach no longer caused the faster heart beat. The original and the control observations were made on the same animals. Repeated tests (excitement, struggle) on these animals further confirm the conclusion that adrenal inactivation alone explains the absence of rise in pulse rate. The faster rate of the denervated heart, therefore, which appears when there is danger that the body temperature will fall, is due to an increased secretion from the adrenal medulla.

THE COMPENSATORY CALORIGENIC EFFECT OF ADRENAL SECRETION EVOKED BY COLD. In a review of the literature Boothby and Sandiford (1923) have called attention to the work of various observers, beginning in 1906, who have noted that administration of adrenalin causes increased oxygen consumption or increased metabolism of isolated organs or of the body as a whole. This evidence of a pharmacological action of adrenalin on the rate of oxidation was given a physiological significance when Aub, Forman and Bright (1921, 1922) found that after removal of the adrenal glands, although blood pressure and temperature were unchanged, the metabolic rate dropped as much as 25 per cent below the previous normal level. In animals anesthetized with urethane they discovered that the standard metabolism, which fell promptly after adrenalectomy, could be restored by intravenous injection of adrenalin in approximately the amount per kilo that is produced by reflex stimulation. An increase of metabolism in man, when adrenalin was injected subcutaneously so as to be distributed in the body at about the physiological rate, was reported by Peabody and his co-workers (1918), by Tompkins, Sturgis and Wearn (1919) and by Sandiford (1920); and Boothby and Sandiford (1923) proved that intravenous injections of adrenalin in dogs, in doses which matched the secreting capacity of the adrenal medulla, notably increased the speed of heat production. Since injected adrenalin increases metabolism, and adrenalectomy decreases it, the inferences seemed justified that absence of the medulla and its secretion, rather than absence of the cortex, is responsible for slower metabolic rate after removal of the adrenals; and conversely that secreted adrenin helps to maintain the normal metabolic rate and by a larger output may increase that rate. Definite evidence

in support of the latter inference has been provided by McIver and Bright (1924), who showed that direct nervous and also reflex stimulation of adrenal secretion promptly augments metabolism to a remarkable degree—even as much as 50 per cent.

Evidence presented in the foregoing pages has shown that medulliadrenal secretion is increased when the organism is exposed to the danger of too rapid heat loss, and the testimony just cited proves that adrenin, secreted in natural amounts, is capable of accelerating in the body the heat production. Here are the factors of a physiological reaction the services of which to the organism ought to be demonstrable. We have attempted in two ways to test the capacity of these reactions: we have studied the effect of a certain heat debt on shivering, when the adrenal glands were active or inactive; and we have observed in man the influence of a heat debt on the metabolic rate in the absence and also in the presence of shivering.

** The effect of a heat debt on shivering when the adrenal glands are present or absent.* In discussing the cases summarized in table 1, we pointed out that animals may meet the heat debt which confronts them by combined calorogenic reactions—by a greater discharge of adrenin, as indicated by a greatly increased heart rate, and by shivering. Doubtless there are other factors which may be called into play, e.g., a saving of heat by peripheral vasoconstriction—a process the efficacy of which is much affected by the temperature and moisture of the air. For the present, however, we are considering the response of the adrenal medulla in relation to shivering. In all the animals of table 1, in which this response was examined, the heat debt was large—about 2000 calories per kilo. Since, even when shivering complicates the reaction to a threatened heat loss, increased medulliadrenal secretion occurs before the shivering begins and may well outlast it, and since the secretion may occur without any shivering whatever, and since the greater output of adrenin results in more rapid metabolism, we should be able to select a heat debt for which the increased secretion would be barely adequate without the help of shivering, and this debt in the absence of the secretion ought, theoretically, to call forth shivering. One might argue that after removal of one adrenal gland the same heat debt per kilo should not be induced as before, because even a single adrenalectomy depresses the metabolic rate (Barlow, 1924). This lowered rate, however, serves to emphasize the importance of the adrenal, in all probability the medullary portion, in the maintenance of a normal heat production. And since the object of our tests was to learn whether in the absence of adrenin the organism would resort to other factors for the heat needed to prevent a fall of temperature we felt justified in keeping the heat debt uniform. The debt which we found to be critical was 900 small calories per kilo. The figure (900 calories) was

TABLE 2

Presence or absence of shivering where there was a heat debt of about 800 calories in (A) cats with normally innervated adrenal glands, and in (B) cats with one adrenal gland removed and the other denervated

A. ADRENALS BOTH INNERVATED										B. ADRENALS, ONE OUT, THE OTHER DENERVATED									
Cat	Date	Temp of room	Weight of cat	Amount of water	Temp of water	Shiver	Remarks	Cat	Date	Temp of room	Weight of cat	Amount of water	Temp of water	Shiver	Remarks				
116	Feb. 14	22	3.9	98	0.2	0*	Lean	263	Feb. 14	21.6	3.5	83	0.3	0					
A	Feb. 21	19.5	2.9	70	0.0	0	Med. fat	233	Feb. 18	21.8	3.4	82	0.5	15					
B	Feb. 21	19.7	3.1	75	0.1	3	Lean	110	Feb. 19	19.5	2.9	70	0.5	3	Med. fat				
C	Feb. 21	19.8	3.8	92	0.2	0	Sl. fat	90	Feb. 19	19.7	3.2	78	0.1	7	Med. fat				
D	Feb. 21	19.8	3.2	77	0.1	0	Lean	112	Feb. 19	19.7	4.0	98	0.1	0	Med. fat				
E	Feb. 21	20	3.5	85	0.1	0	Med. fat	116	Feb. 19	19.7	3.9	97	0.2	17*	Lean				
F	Feb. 21	20	3.7	90	0.2	0	Very lean	109	Feb. 19	20.4	3.3	80	0.7	6					
G	Feb. 21	20	2.8	68	0.0	3	Very lean	90	Mar. 22	21.0	3.0	73	0.2	8	Med. fat				
H	Feb. 21	20.2	4.0	97	0.2	0	Med. fat	110	Mar. 22	21.0	2.7	65	0.4	3	Med. fat				
244	Apr. 9	21	1.95	47	0.4	0*	Lean	110	Apr. 7	20.5	2.9	70	0.3	4	Med. fat				
I	Apr. 11	20.5	2.8	68	0.7	0	Lean	112	Apr. 7	21.0	4.0	97	0.2	13	Med. fat				
J	Apr. 11	21	2.6	63	0.5	0		90	Apr. 7	21.0	3.1	75	0.2	5	Med. fat				
K	Apr. 11	21	3.5	85	0.5	0	Med. fat	240	Apr. 7	21.0	4.0	97	0.4	16	Lean				
L	Apr. 11	21	3.2	78	0.3	0	Med. fat	244	Apr. 22	21.5	2.05	50	0.4	11*	Lean				
M	Apr. 22	21.5	3.5	85	0.2	0	Med. fat	240	Apr. 22	22.0	4.0	97	0.3	16	Lean				

*The same animals before and after inactivation of the adrenal glands.

reached after some preliminary tests above and below it. The animals had been fed the previous afternoon. They were observed in a routine manner after cold water was introduced into the stomach. They were placed on a table where, with hairs bristling, they usually crouched in a huddled position. A nearby thermometer showed the temperature of the room. The animals were not touched. They were carefully watched for shivering (a response which, if it occurred, was readily recognized by the quivering of the erect hairs) until the reaction passed. In different animals and at different times there was considerable variation in the degree of spread of the shivering reaction over the body.

As shown in table 2 a heat debt of 900 small calories rarely causes shivering in animals having intact adrenals—it occurred in only 2 cases out of 15. Whether the animals were lean or fat made no obvious difference in the responses. That the sympathetic system was active in these cases was indicated by the bristling hairs along the back. Under such conditions, as previously shown, the adrenal medulla is stimulated to extra secretion. Even when shivering did appear, it lasted only a short time. In the first of the two instances in section A, table 2 (B, Feb. 21), there was slight shivering of the hind legs at 10:30, that had become vigorous and spread over the whole body a minute later and that had quite passed off by 10:33; in the second instance (G, Feb. 21), a slight shivering was noted at 3:18, that had disappeared by 3:21. On the other hand, after the adrenal factor in heat production had been eliminated by removal of one gland and denervation of the other, the same heat debt caused shivering in 13 cases out of 15 observations, and furthermore, the shivering usually lasted for periods considerably longer than in the control series—for 6, 7, 8, 11, 13 and even 16 and 17 minutes instead of 3 minutes. The animal in section B, table 2, that shivered for 17 minutes on February 19 was the same animal that was recorded in section A, table 2, as not shivering at all on February 14; the adrenals were inactivated on February 16. Compare also the record for April 9 (no shivering) and that for April 22 (shivering for 11 minutes); these results were obtained on the same animal and the difference between them may be accounted for by the inactivation of the adrenal glands on April 12. In some of the tests preliminary to the selection of 900 calories as a standard heat debt the animals with intact adrenal glands met the demand for approximately 1000 calories per kilo without shivering whereas one of the animals deprived of the adrenal factor shivered for 11 minutes when confronted with a heat requirement of 840 calories per kilo.

Our previous observations have shown that when an animal has to develop heat to prevent lowering of body temperature it may rely both on the calorogenic effect of increased adrenal secretion and on the extra heat accompanying reflex muscular contractions. The results just de-

tailed indicate that the primary protection against a heat deficit is found in activities of the sympathetic system (bristling of hairs, probably vasoconstriction and hyperglycemia, and surely by increased medulliadrenal secretion), for these responses occur before the onset of shivering, and may be the only manifestations of a heat debt. If animals have been deprived of the calorogenic service of the adrenal medulla, however, greater demands are made on muscular activity as a means of maintaining the normal temperature—then, in the presence of a given need for heat, shivering occurs more frequently and lasts longer. The non-use of the shivering mechanism, or the relatively slight reliance on it when the adrenals are present, implies that the secretion poured out by them when the organism is in danger of cooling is an efficient means of increasing heat production.

The influence of heat debt on the metabolic rate, independent of shivering. Since a sufficient heat debt will evoke increased adrenal secretion without attendant shivering, and since increased adrenal secretion markedly accelerates metabolism, it should be possible to demonstrate a faster metabolic rate in response to the bodily need for heat, and this quite apart from any muscular quiverings or contractions. In order to secure evidence on this point we have studied the change in the metabolic rate when a known heat debt was created by giving cold water (1° or colder) or cold water and ice. The subjects were men and women—students and workers in the laboratory—who were in vigorous health. The determinations of the metabolic rate were made in the morning before breakfast. After the subject had rested on a couch for a half-hour, two or three preliminary tests were made. One subject (A. Q., table 3) took the cold water by stomach tube. While still lying on the couch he allowed the tube to be passed; and then the water, which had been measured previously and which was kept cold in a flask set in an ice-salt mixture, was quickly poured into a funnel at the top of the tube. As soon as the water had run out of the funnel the tube was withdrawn. At first there was considerable disturbance due to this procedure but after a few trials the subject became accustomed to it and the difficulty largely disappeared. In other determinations it was found that the water could be taken fairly quickly by being siphoned through a tube reaching from the elevated flask to the subject's lips. In some instances the heat debt due to the cold water was increased by swallowing small lumps of ice which were placed in the subject's mouth from a spoon (see table 3). Usually three or four minutes elapsed after the water or water and ice were administered before the series of determinations was started. Thereafter the subjects did not complain of any discomfort, though in three instances there was testimony of a sensation as of a cold wave sweeping over the back, associated with the phenomenon of "goose flesh," i.e., the equivalent of erection of hairs and indicating activity of the sympathetic system. In three of the thirty-

TABLE 3

Records of the increase of the metabolic rate (without shivering) when a heat debt was established by cold water taken into the stomach, and of the absence of such increase when similar amounts of warm water were taken (italicized figures). Calculations based on general body temperature of 33° (see auxiliary temperatures, tables 4, 5 and 6)

DATE	SUBJECT	SEX	AGE	WEIGHT kgrm.	HEIGHT mm.	TEMPERATURE OF ROOM °C.	AMOUNT OF		HEAT DEBT cal./kgrm.	METABOLISM CAL./SQ.M./HR.		TIME OF MAXIMUM METABOLISM AF- TER H ₂ O	INCREASE IN METAB- OLISM per cent	REMARKS
							Ice	H ₂ O		Prelim- inary	Maxi- mum	min.		
1/22/25	S. W. B.	♂	32	73.0	177.0	14.4	143	520	476	41.1	53.0	17	28.5	Very low room temperature. Shivering later
2/ 4/25	S. W. B.					21.0	150	375	418	38.5	42.7	27	11.0	Control, 600 cc. H ₂ O at 25.0°C.
5/25/25	S. W. B.					19.5		600	98	39.5	41.8	7	5.8	
10/25/24	D. E. S. B.					20.0	150	482	496	36.3	46.4	20	27.7	
11/11/24	D. E. S. B.	♂	23	70.0	182.0	22.7	153	463	492	37.8	43.6	31	15.4	
2/ 2/25	D. E. S. B.					20.0	148	391	435	38.8	42.7	23	10.0	
4/ 5/25	D. E. S. B.					22.7	140	543	472	38.7	44.6	30	15.2	
7/17/25	D. E. S. B.					26.5		557	47	35.7	37.8	6	6.0	Control, 557 cc. H ₂ O at 30.0°C.
5/13/25	R. W. D.					21.8	142	346	444	38.1	49.4	18	29.8	
6/11/25	R. W. D.	♂	22	65.8	171.0	23.5		490	45	41.1	41.4		0.0	Control, 490 cc. H ₂ O at 30.0°C.
6/30/25	A. J. E.	♀	29	60.0	168.7	24.5		420	43	32.0	33.7	7	5.0	Control, 420 cc. H ₂ O at 30.2°C.
6/20/25	A. J. E.					25.0	139	260	424	30.4	34.6	28	14.0	Immediately following control

4/15/25 5/26/25 5/26/25	J. L. H. J. L. H. J. L. H.	♀	25	68.8 68.0	164.5	20.5 19.5 20.0	120	400 520 354	384 46 409	30.6 35.0 35.1	34.0 36.4 39.9	24 8 27	11.0 4.0 13.7	Control. 520 cc. H ₂ O at 30.0°C. Very slight shivering pre- vious to the period used in calculating the maximum rise
8/ 4/25	J. T. L.	♂	27	66.5	166.5	25.5		500	45	34.7	35.2	7	1.0	Control. 500 cc. H ₂ O at 30.0°C.
9/28/25	J. R. L.	♂	26	72.0	177.5	22.8		650	49	37.7	39.2	11	3.4	Control. 650 cc. H ₂ O at 30.5°C.
9/28/25	J. R. L.					24.5	138	335	389	37.6	43.2	10	15.0	
10/23/24 11/ 4/24 2/19/25 6/27/25	R. R. L. R. R. L. R. R. L. R. R. L.	♂	24	74.0	179.2	18.4 20.5 19.0 23.0	148 148	740 576 337 600	350 512 385 49	39.2 40.0 39.6 40.1	43.1 43.4 43.9 39.6	32 25 25 8	10.0 8.4 11.0 -1.3	Steady drop in metabolism after 39.6
6/ 4/25 4/14/25 5/27/25	J. D. P. J. D. P. J. D. P.	♂	22	59.0	169.0	28.0 21.0 20.0	145 130	595 430 623	527 485 63	38.6 40.4 38.9	41.9 55.7 40.7	24 14 14	8.5 38.0 4.8	High room temperature "No shivering." Subject very quiet Control. 623 cc. H ₂ O at 30.0°C.
1/16/24 1/22/24 1/25/24 2/ 5/24 2/ 2/24	A. Q. A. Q. A. Q. A. Q. A. Q.	♂	23	54.2	156.0	21.0 18.5 21.2 24.0 22.5		750 665 750 750 750	471 441 484 498 21	37.1 37.8 37.9 36.8 41.5	42.7 45.8 43.1 46.3 43.8	21 34 23 16 11	15.0 21.0 14.0 25.0 5.4	Slight shiver 14 minutes after water Control. 750 cc. H ₂ O at 34.5°C.
10/22/24 3/12/25 7/28/25	A. T. A. T. A. T.	♀	49	67.2 66.0	171.3	20.0 21.5 19.0 24.0	150 117	450 355 600	483 383 58	35.5 33.6 31.3	40.3 38.2 31.5	26 32 9	13.5 13.6 0.5	Control. 600 cc. H ₂ O at 29.6°C.

TABLE 4

Complete records of two subjects in whom a heat debt was met by increased metabolism without shivering. The figures for the control records are italicized. The axillary temperatures are in parentheses

DATE	SUBJECT	TEMPERATURE OF ROOM	HEAT DEBT	METABOLISM—CAL. PER SQ. M. PER HOUR								TIME OF MAXIMUM METABOLISM AFTER H ₂ O	INCREASE IN METABOLISM
				Preliminary	I	II	III	IV	V	VI	VII		
°C.	cat./kgm.											min.	per cent
10/23/24	R. R. L.	18.4	350	39.2 (36.3)	41.5 (35.4)	42.1 (35.6)	41.9 (35.8)	43.1 (35.8)	41.1 (35.8)	42.5 (35.9)	39.7 (36.0)	32	10.0
11/ 4/24	R. R. L.	20.5	512	40.0 (36.4)	41.3 (36.0)	40.8 (35.9)	43.4 (35.9)	41.9 (36.0)	41.6 (36.0)	40.4 (36.0)	40.1 (36.1)	25	8.4
2/19/25	R. R. L.	19.0	385	39.6 (36.2)	40.8 (36.0)	42.4 (35.8)	43.9 (35.7)	42.3 (35.6)	43.2 (35.7)	41.0 (35.7)	41.3 (35.7)	25	11.0
6/27/25*	R. R. L.	23.0	49	40.1 (36.6)	39.6 (36.6)	39.6 (35.6)	38.6 (36.6)	37.2 (36.6)				8	-1.3
10/25/24	D. E. S. B.	20.0	496	36.3 (36.3)	43.5 (35.1)	46.4 (34.7)	42.3 (34.8)	42.3 (35.2)	41.5 (35.4)	39.5 (35.5)		20	27.7
11/11/24	D. E. S. B.	22.7	492	37.8 (36.4)	39.5 (35.8)	41.1 (35.9)	39.5 (35.9)	43.6 (36.0)	41.3 (36.0)			31	15.4
2/ 2/25	D. E. S. B.	20.0	435	38.8 (36.4)	39.7 (35.6)	39.9 (35.5)	42.7 (35.4)	39.7 (35.4)	39.6 (35.2)			23	10.0
4/ 5/25	D. E. S. B.	22.7	472	38.7 (36.4)	40.3 (36.0)	40.0 (36.0)	41.5 (36.1)	44.6 (36.0)	38.5 (36.0)	40.9 (36.1)	40.0 (36.2)	30	15.2
7/17/25†	D. E. S. B.	26.5	47	35.7 (36.3)	37.8 (36.3)	37.8 (36.3)	36.5 (36.3)					6	6.0

* Control. 600 cc. water at 30.2°C.

† Control. 557 cc. water at 30.0°C.

three determinations reported in table 3 (S. W. B., Jan. 22; J. L. H., May 26; and A. Q., Jan. 22) there was slight shivering, but not during the period used for comparison with the preliminary basal period. The body temperature was taken in the axilla because the mouthpiece excluded use of the buccal region and because cold water in the abdomen might produce a local temperature change in the rectal region. The chief defect of the method was an onset of restlessness 50 or 60 minutes after the water was given, due to tension of the urinary bladder. Since the maximal changes of metabolism occurred well within this time, however, the restlessness did not disturb the essential conditions of the experiment.

The metabolism was measured by oxygen consumption alone. The Benedict apparatus as modified by Roth (1923) was used to determine the rate of oxygen utilization. The record of the movement of the oxygen cylinder was written on a smoked drum. As recommended by Roth, the single periods lasted a little longer than six minutes. The metabolism of the subject, in calories per square meter per hour, was calculated by the Du Bois formula.

It should be clearly understood that these experiments on human subjects were in all respects equivalent to those on lower animals in which the heat debt, without evoking shivering, augmented the output of adrenin—a calorigenic agent.

In table 3 are presented the main data of 33 tests on 11 subjects. The detailed data of the several periods in 4 tests on R. R. L. and in 5 tests on D. E. S. B. are given in table 4. And the original records for the preliminary period and for periods II and VI of the experiment on D. E. S. B. October 25, 1924, are reproduced in figure 5. Examination of tables 3 and 4 reveals the usual differences to be noted between the taking of cold water, or a combination of cold water and ice, which establishes a considerable heat debt, and the taking of an approximately equivalent amount of water at a temperature which makes no noteworthy demand for extra heat production. Except in one case which was defective, the lowest figure for the estimated calories per square meter of body surface in the preliminary tests was taken as basal. The average heat debt established in 22 cases was 449 small calories per kilo, with variations between 350 and 527. In these cases the average increase of metabolism during the period of greatest effect was 16.4 per cent, with variations between 8.4 and 38. There was no close relation between the amount of the heat debt and the increase of metabolism, though in four cases, in which the debt was below 400 (averaging 375 calories per kilo), the average increase of metabolism was only 11.4 per cent. On the other hand the two lowest increases, 8.4 and 8.5 per cent, occurred when the debt was more than 500 calories per kilo. In one of these cases, the room tem-

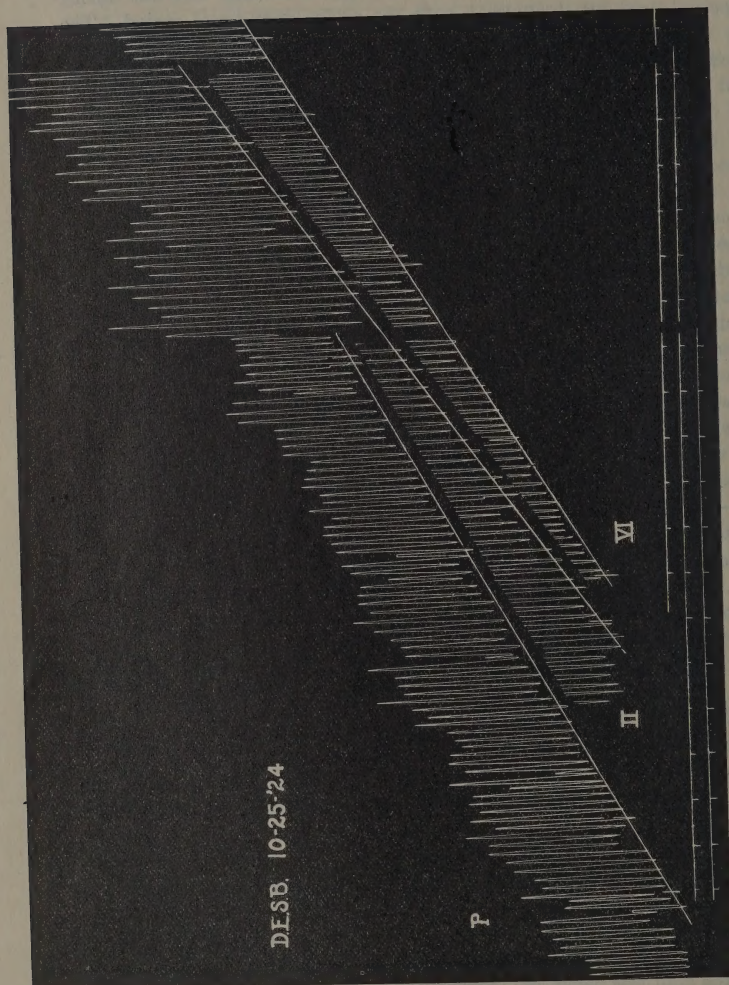


Fig. 5. Records of the preliminary period, *P*, and of periods II and VI of the observations on D. E. S. B., October 25, 1924 (see table 4). Windows have been cut in *P* and II to permit the base line of the underlying records to be seen. Time in half-minutes. In each case the record ran for at least six and a half minutes. Original record reduced one-third.

perature was unusually high (28°), a circumstance the importance of which has already been noted and which will be further emphasized later; and in the other case there may have been a depressed condition such as occurs occasionally and may occur regularly, in which cold is not reacted to (see p. 496). The greatest increases were seen when the debt was between 400 and 500; in sixteen such instances it averaged 18.6 per cent.

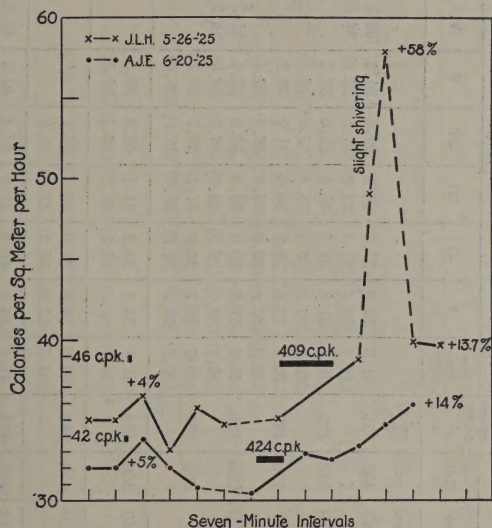


Fig. 6. Changes in metabolism produced by taking warm water and later by taking cold water and ice. A heat debt of 46 small calories (per k.) due to taking 520 cc. of water at 30° caused in J. L. H. an immediate increase of 4 per cent in the metabolic rate; a heat debt of 409 calories from taking 354 cc. of water at 1° and 130 g. of ice caused an increase of 13.7 per cent. Slight shivering was attended by a sudden and temporary increase of 58 per cent. A heat debt of 42 calories from 420 cc. of water at 30.2° caused in A. J. E. an immediate increase of 5 per cent in the metabolic rate; a heat debt of 424 calories, from 260 cc. of water at 1° and 139 g. of ice, caused a gradual increase of 14 per cent, without shivering. Each point breaking the line represents a metabolism record.

Although in all these instances there was, of course, some disturbance of the subject when the cold water was given, the time of highest metabolism was not immediately thereafter, but regularly much later—averaging 23 minutes, i.e., in the third or fourth period.

The results of control observations were markedly different. The water was given at a temperature near 30° . The average heat debt in

TABLE 5
Cases of depression of metabolism caused by a heat debt. The axillary temperatures are reported in parentheses

DATE	SUBJECT	SEX	AGE	WEIGHT kgm.	HEIGHT mm.	TEMPERATURE OF ROOM °C.	AMOUNT OF		HEAT DEBT cal./ kgm.	METABOLISM—CAL. PER SQ. M. PER HOUR										MAXIMUM DEPRESSION BELOW BASAL per cent	MAXIMUM RISE ABOVE BASAL per cent
							Ice	H ₂ O		Pre- limi- nary	I	II	III	IV	V	VI	VII				
																		cc.	cal./ kgm.		
10/18/24	E. M. B.	♀	32	64.0	172.0	19.5	147	452	521	31.3 (35.9)	32.0 (35.3)	27.4 (34.9)	30.8 (34.8)	29.7 (34.8)	31.1 (34.9)	30.7 (34.9)	31.9 (34.9)	-12.5	+0.0		
10/30/24	E. M. B.					22.5	138	413	476	32.1 (36.2)	31.3 (36.2)	31.5 (36.0)	33.4 (35.9)	32.6 (35.9)	32.3 (35.9)			-2.5	+4.0		
2/19/25	E. M. B.					20.0	147	420	489	30.2 (36.0)	32.6* (36.1)	29.9 (36.0)	30.4 (35.9)	31.9 (36.0)	33.2 (36.0)			-1.0	+10.0		
3/17/25	E. M. B.					19.5	120	226	323	31.8 (36.1)	31.6 (36.0)	29.9 (36.0)	32.3 (36.0)	33.9 (36.0)	33.4 (36.0)	31.2 (36.0)	30.5 (36.0)	-6.0	+6.5		
5/19/25†	E. M. B.					22.8		603	160	29.6 (36.2)	28.7 (36.0)	28.0 (36.0)	31.1 (36.0)	29.7 (36.0)	28.7 (36.0)			-5.5	+5.0		
10/ 7/24	S. W. B.	♂	32	73.0	177.0	21.5	136	500	464	41.1 (36.6)	34.1 (36.4)	34.2 (36.3)	41.1 (36.3)	43.4 (36.4)	39.5 (36.5)			-17.0	+5.6		
4/15/25	J. L. H.	♀	25	68.0	164.5	20.5	120	400	384	30.6 (35.5)	29.9 (35.8)	34.0 (35.8)	33.2 (35.8)	33.1 (35.8)				-2.4	+11.0		
3/17/25	J. R. L.	♂	26	73.8	177.5	19.2	143	495	435	41.5 (35.6)	35.9 (36.0)	40.3 (35.9)	41.8 (35.8)	43.4 (35.7)	40.3 (35.8)	42.5 (35.8)	38.5 (35.7)	-13.5	+4.5		

* Rise due to activity of taking ice and H₂O.

† Control.

TABLE 6

Cases showing the marked increase of metabolism which occurs when shivering appears. The presence of shivering is indicated by an asterisk (*). The axillary temperatures are reported in parentheses

DATE	SUBJECT	SEX	AGE	WEIGHT kgm.	HEIGHT mm.	TEMPERATURE OF ROOM °C.	AMOUNT OF		HEAT DEBT cal./ kgm.	METABOLISM—CAL. PER SQ. M. PER HOUR							TIME OF MAXIMUM METABOLISM AF- TER H ₂ O	per cent INCREASE IN METAB- OLISM	
							Ice	H ₂ O		Pre- limi- nary	I	II	III	IV	V	VI			VII
1/29/25	E. M. B.	♀	32	64.0	172.0	16.6	gms. 145	cc. 545	565	31.4 (36.2)	36.4 (35.9)	41.3* (35.9)	37.4 (35.9)	34.0 (35.9)	32.1 (35.8)	30.5 (35.8)	31.3 (35.7)	18	31.5
1/22/25	S. W. B.	♂	32	73.0	177.0	14.4	143	520	476	41.1 (36.7)	53.0 (36.25)	59.1 (36.25)	79.7* (36.35)	67.8 (36.5)	67.1 (36.6)	52.8 (36.7)	40.3 (36.75)	29	94.0
3/14/25	A. J. E.	♀	29	60.0	168.7	20.0 18.0	161	266	464	32.9 (36.0)	46.9* (35.7)	38.0* (35.5)	37.2 (35.5)	36.1 (35.5)	36.6 (35.5)	35.6 (35.5)		7	42.2
3/23/25	A. J. E.					19.0	150	272	453	31.9 (36.3)	42.3* (35.3)	42.7* (35.6)	39.1* (35.65)	38.2 (35.7)	36.7 (35.8)			5	34.0
2/ 2/25	A. T.	♀	49	66.0	171.3	18.6 17.0	147	435	492	35.7 (36.0)	42.1 (36.3)	43.5* (36.1)	46.5* (36.0)	41.7 (36.0)	?	35.8 (35.9)		23	30.2
1/22/24	A. Q.	♂	23	54.2	156.2	18.5		665	454	37.8 (37.2)	40.4 (37.2)	60.0* (36.9)	52.1* (36.8)	44.7 (36.8)	45.8 (36.8)	41.2 (36.8)	42.9 (36.8)	14	59.0

11 cases was 50 small calories per kilo, a little more than a tenth of the debt when the cold tests were made. In one case no change of metabolism occurred, in another it fell 1.3 per cent; and the average of all the cases was an increase of only 3.1 per cent. Furthermore, this increase was probably largely caused by the disturbance due to taking the water, for in all but one case it came in the first period thereafter, instead of the third or fourth period, which was the time of highest metabolism after the cold intake. In three cases the control observations were followed in a short time by observations on the effects of cold water—A. J. E., June 20; J. L. H., May 26; and J. R. L., September 28, in table 3. The results in two cases are displayed graphically in figure 6. In these three instances the taking of warm water, comparable in amount with that taken as cold, resulted in only relatively slight increases of metabolism; whereas the taking of cold water and ice after a short period of rest, but otherwise under the same circumstances, resulted in typical accelerations of the metabolic rate.

The phenomenon of depression, or of failure to "react," after exposure to cold (e.g., after a cold bath) is well known. In one of the subjects (E. M. B.) depression, in the sense of feeling miserable and ill and also in the objective sense of a lowered metabolic rate, was a characteristic result of taking ice and ice water. The figures for the tests made on her are given in table 5. It will be noted that in the one test in which she showed clear acceleration of metabolism she shivered (see table 6). It is noteworthy also that she had an abnormally low metabolic rate—in six tests varying only slightly from an average of 31 calories per square meter per hour, which was 15 per cent below the standard. Compare also J. L. H. in tables 3 and 5. On the other hand, even in persons who usually reacted to the heat debt by prompt responses which were directed towards payment, the metabolic rate might be depressed in occasional experiments, as shown in the other subjects of table 5. In all these cases the depression was temporary, and was followed by a rise of metabolism, often to a level well above that which prevailed in the preliminary (basal) period.

Table 6 is presented to show that when shivering occurs the metabolic rate is, usually, much more strikingly accelerated than when, as in the cases shown in table 3, it is absent (see also J. L. H. in figure 6). Shivering causes a marked and sudden increase of metabolism, an increase which may be as much as 60 or 90 per cent above the basal rate. In the observation on E. M. B. January 29, 1925, the increase of 31.5 per cent does not appear great as compared with the increases in the other subjects. The results in that instance, however, should be compared with those from E. M. B. in table 5. It will be seen that her most characteristic reaction to the cold was depression. The increase of 31.5 per cent when

TABLE 7
Cases showing the influence of external temperature on the efficacy of a heat debt in causing increase of metabolism. The axillary temperatures are reported in parentheses

DATE	SUBJECT	TEMPERATURE OF ROOM °C.	HEAT DEBT cal./kgm.	METABOLISM—CAL. PER SQ. M. PER HOUR						TIME OF MAXIMUM METABOLISM AFTER H ₂ O min.	INCREASE IN METABOLISM per cent
				Preliminary	I	II	III	IV	V	VI	
10/28/24	J. R. L.	25.0	450	37.0 (36.1)	37.0 (35.8)	37.7 (35.8)	37.2 (35.8)	37.6 (35.7)	38.2 (35.7)	38.8 (35.8)	
1/22/25	J. R. L.	14.0	470	39.0 (35.8)	46.9* (35.4)	44.3* (35.5)	46.3* (35.5)	48.8 (35.5)	50.9 (35.5)		30.0
10/30/24	S. W. B.	23.3	480	43.4 (36.4)	43.8 (36.1)	43.8 (36.1)	44.4 (36.0)	44.4 (36.0)	43.9 (36.1)	42.1 (36.1)	2.4
1/22/25	S. W. B.	14.4	476	41.1 (36.7)	53.0 (36.25)	59.1† (36.25)	79.7† (36.35)	67.8† (36.5)	67.1† (36.6)	52.8 (36.7)	28.5†
6/ 4/25	J. D. P.	27.7 { 28.5	527	39.4 (36.4)	40.3 (36.2)	40.4 (36.1)	41.9 (36.1)	38.6 (36.1)	39.4 (36.3)		6.2
4/14/25	J. D. P.	20.0 { 21.5	485	40.4 (36.4)	41.4 (36.0)	47.8 (36.0)	55.7 (36.0)	52.9 (36.0)	48.0 { 43.3 (36.1)	41.8 (36.2)	38.0

* "Waves of cold" felt in back. No shivering observed.

† Shivering.

‡ Calculated on 53.0.

she shivered was quite remarkable. The increase of 30 per cent shown by A. T. during shivering was more than twice that shown by her when she did not shiver (see table 3).

If the external air is colder than the body there is, of course, a flow of heat to it from the body—a flow which is controlled to a large extent by the degree of exposure of warm blood in surface vessels. There is evidence that when conditions tend to lower body temperature the surface vessels are contracted (Tigerstedt, 1923). Thus heat is conserved. When a heat debt is established by taking cold water and ice, the debt may be at least partially paid by retaining the heat which otherwise would be lost through the skin. If the external air is sufficiently cold, however, the agencies for heat conservation may already be working at a maximum. In that event the only manner of meeting the debt would be by extra heat production. The condition is quite otherwise if the external air is warm and the surface vessels are dilated in order to increase the heat loss. In these circumstances, extra heat production may not be necessary if the escaping heat is saved and applied to paying the debt. In cold surroundings, therefore, a given heat debt might be expected to cause a much greater increase of metabolism than it would cause in warm surroundings. That such is the case is shown in table 7. In the case of J. D. P., for example, a heat debt of 527 calories per kilo increased the metabolism only 6.2 per cent when the temperature of the air was about 28°, whereas a debt of 485 calories induced an increase of 38 per cent when the temperature was about 21°. In the cases of J. R. L. and S. W. B. in table 7, "waves of cold" or shivering were induced by the heat debt, and the metabolism was markedly increased even in the absence of these conditions when the external temperature was low; whereas nearly the same heat debt had no such effects when the external temperature was 9° to 11° higher. It is evident that there may be difficulty in obtaining such results as are reported in table 3 if the experiments are carried on in very warm surroundings.

The results of our studies on cats showed that a considerable heat debt, which fails to cause shivering, still causes an increased discharge of adrenin, that when shivering occurs the extra adrenin output precedes it, and that when adrenin is excluded from action the organism resorts to shivering as it does not when adrenin is present. These observations disclose the importance of adrenin as a calorogenic factor and indicate that for the chemical increase of heat production the organism relies upon the adrenal medulla primarily. Adrenin acts by raising the metabolic rate. In the foregoing experiments on human subjects (table 3) the metabolic rate was raised, without shivering, under conditions precisely resembling those which evoked in lower animals a greater adrenin discharge. We conclude, therefore, that in man as well as in lower animals

the adrenal medulla is stimulated by a threatened fall of body temperature and that its secretion, by hastening combustion, acts to avert the danger.

DISCUSSION. Rubner (1902, p. 221) has defined chemical regulation of body temperature as the maintenance of the normal temperature by "increase of heat production in the resting animal." For many years there has been a controversy concerning a true chemical regulation in Rubner's sense. One group of investigators has contended that the increase of heat production in time of need is wholly due to the effects of shivering or of greater muscular tension, i.e., the animal is not "resting." The other group has maintained that an increased heat production may occur with no muscular activity whatever to account for it.

The view that chemical regulation of temperature is accomplished solely by the additional metabolism that results from shivering or other muscular contraction has been supported by Speck, by Loewy, by Johansson, and by Sjöström. Speck (1883) placed himself in water at 20–21.5°C. for 10 to 12 minutes and recorded his respiratory exchange; he inhibited all muscular action and then observed no certain influence of the external cold on his metabolism. Loewy (1890) made 55 observations on 16 persons who for 2.5 to 3 hours were exposed to cold. The oxygen consumption was constant in 20 cases, was less in 9, and was greater in 26 (47.3 per cent). The body temperature fell in nearly all the tests and there was a sensation of cold. Whenever the oxygen consumption was unchanged or decreased, there was complete quiet. Of the 26 instances of greater oxygen usage, in 13 there was obvious shivering, in the other 13 Loewy suggested, as possibly accounting for the results, unobserved shivering, minor muscular contractions, or continuous slight tensions without visible movements. It is noteworthy that in one instance an increase of 33.3 per cent occurred in the oxygen utilization without visible shivering. Loewy's conclusion, however, was that extra heat production, if called forth by cooling, is dependent on muscular activity. In the experiments of Johansson (1897) the CO₂ output was measured as subjects were exposed to cold air in a respiration chamber. The tests on himself lasted 2.25 hours—a half-hour as a preliminary period, a quarter hour for undressing, *one hour* for exposure, naked, to the cold (12.6° to 18° on different occasions), and a half-hour as an after-period, dressed. The average CO₂ output per hour was greater during the cold period than before or after, but not in accordance with the temperature differences. Shivering occurred during some of the tests and then the output might be increased to threefold that of the preliminary period. When all muscular movements were voluntarily suppressed, Johansson states, no sign of chemical heat regulation was observable. He concluded that chemical heat regulation without muscular contraction does not exist.

Sjöström (1913) using the method employed by Johansson, and studying, on clothed or naked subjects, only those responses which occurred reflexly or automatically during a two-hour exposure to cold air, found that the metabolism, as measured by the CO_2 elimination, is independent of external temperature, so long as shivering is absent. When shivering occurs it increases the CO_2 production somewhat, but the greater oxidation represented by it may not be sufficient to prevent a considerable drop in body temperature. Since shivering may appear suddenly after a brisk cold douche when a noteworthy fall of temperature cannot have taken place, or may appear when one removes one's clothing and still has a rectal temperature within the normal range of variation, Sjöström argues that shivering is a reflex initiated by the cold receptors, and that therefore the temperature conditions of the skin are decisive for its onset.

Opposed to the evidence that all chemical regulation of heat production involves muscular movement are the observations of Voit and of Rubner. Voit (1878) reported experiments on a clothed man in the condition of basal metabolism who was exposed for six hours to temperatures ranging between 4.4° and 30° ; at the end of the experiment with the lowest temperature (4.4°) he shivered, but the CO_2 output at 6.5° , without shivering, averaged 8.5 grams per hour more than at 14.3° . Voit argued against explaining this effect by reflex excitatory influence on respiration, and attributed it to a stimulating action of the nervous system on muscular metabolism similar to that occurring in muscular work (Voit, 1881). Voit's results were confirmed by Rubner and Lewaschew (1897) in tests on subjects who rested quietly from *five to eight hours* in surroundings where the temperature and water vapor could be controlled. They found that 32.34 grams of CO_2 per hour were given off in dry air at 15° , as contrasted with 27.9 grams at 23° ; and in moist air at the same temperatures 34 grams as contrasted with 28.61 grams. Rubner also reported similar observations on dogs. In one instance, for example, the heat production rose from 64.5 Calories per kilo for 24 hours at 31° to 83.1 Calories at 15.5° and to 120.5 Calories at 7.3° . He comments (1902, p. 138): "It is incomprehensible that many physiologists can still doubt the presence of this powerful regulating mechanism. And it is just as incomprehensible that the increase of heat in the presence of cold is ascribed solely to the gross shivering of the animal. Will anybody assume that animals which show chemical regulation at 30° begin to shiver at 29° , 28° , etc., when they withstand a temperature of 0° without any visible disturbance?" The most recent supporters of the view that there is a true chemical stimulant of metabolism when extra heat is needed are Leonard Hill and his collaborators (1921). They exposed subjects to surroundings which had different cooling powers, but did not permit the cooling to continue to the point at which shivering appeared. The ex-

pired air was collected and analyzed. The data thus obtained showed that the metabolism was increased directly with the cooling effects of the atmosphere.

Here is a sharp difference of evidence and of inference that demands explanation. What may be said regarding the contradictory results?

1. The experiments said to prove that shivering is essential to increased heat production are not wholly consistent, and therefore not decisive. This is a criticism which Rubner made with reference to both Loewy's and Johansson's studies. Of Loewy's 55 cases we need consider only those in which cold increased the metabolism, as shown by a greater oxygen usage. In 50 per cent of these cases there was no obvious shivering; Loewy had to *assume* that muscular contractions and tensions were present—he did not prove their existence. If they were not present the augmented metabolism must have been due to some other factor. Again, in Johansson's personal experiments, although a three-fold increase of the CO_2 output was associated with shivering in one instance (a degree of effect never observed by Rubner), considerable increases over the figures for the preliminary period—as much as 11 and 28 per cent—were reported, with testimony that there was "no shivering." Sjöström's observations, likewise, revealed a larger output of carbon dioxide during the second hour of exposure to cold—in one case a rise of 7 per cent, in another 14 per cent, without shivering to account for it. It is clear that such conditions as these, occurring in the work of investigators who have interpreted their results as demonstrating that chemical increase of heat production without muscular contraction does not exist, permit us to question that conclusion.

2. The presence of shivering does not exclude the additional presence of a pure chemical stimulus to extra heat production. Indeed, as shown in figure 1, chilling an animal with cold air may cause shivering, but simultaneously the chilling augments adrenal secretion, as shown by acceleration of the denervated heart. Indeed, all our evidence supports the conclusion that when conditions are such as to induce shivering, they are also such as to induce a faster rate of adrenal secretion. Extra heat production as a consequence of a larger output of adrenin would therefore coexist with the extra heat production due to muscular activity. This fact at once vitiates the conclusion that shivering alone accounts for the chemical regulation of body temperature.

3. Subjects exposed to cold for *short* periods, and subjects who, having become "hardened," do not react to cold as formerly, may not shiver when exposed to heat loss and may not manifest any other sign of faster metabolism. It is noteworthy that both Voit's and Rubner's experiments lasted many hours, while those of their opponents lasted a much shorter time. As Rubner has pointed out, in *short* experiments there may

not be sufficient heat loss to call the calorigenic apparatus into action. It seems to us that this condition is especially apt to occur in such experiments as Speck's in which the body is exposed to cool surroundings for only a few minutes. Further, the specific heats of air and the body are so different that *long* experiments in cold air might be required before the mechanisms for augmenting heat would be set in operation. Especially would this be true as the subjects became accustomed to the cold surroundings. Both Loewy and Johansson noted this "hardening" of their subjects, so that an external temperature that at first caused marked shivering later had no effect at all. The nature of this adaptation is not clear. It may be an adjustment of the skin receptors so that they become less sensitive to external cold; it may be a better and quicker action of the vasoconstrictor mechanism, which, checking the flow of warm blood in the surface vessels, protects the body against heat loss. Whatever its nature, however, it may be associated not only with absence of shivering, but also with absence of true chemical calorigenesis. Then the O_2 intake, as in Loewy's observations, or the CO_2 output, as in the observations of Johansson and Sjöström, may remain almost unchanged during exposure to cold for the relatively short periods of their experiments. Such evidence has the weakness of all negative evidence, and is of little value in the presence of positive evidence to the contrary. In short, the mere fact that the chemical mechanism for producing extra heat is not brought into operation is no proof that it does not exist.

Our criticisms of the opponents of true chemical heat regulation may be summarized as follows: in experiments on the effects of cold they have reported substantial increases of metabolism that had no shivering to account for them; they have failed to recognize that shivering may co-exist with and effectively mask a true chemical calorigenesis; and they have inferred that because a chemical mechanism did not operate in certain short experiments the mechanism does not operate—an inference having slight value when confronted with good evidence to the contrary.

It is obvious that the objections raised against short experiments on the effects of exposing the body surface to cool air or to moderately cool water cannot be raised against our experiments as reported in the foregoing pages. In them a large amount of *cold* water was introduced into the stomach. It has a higher heat capacity per unit quantity than the body itself. It was at or near 0° . It would represent a considerable heat deficit if no reaction should occur. Great vessels and highly vascular organs (the liver and spleen) are near, so that the organism cannot prevent escape of heat into this water, as it can prevent escape of heat into the surrounding cool air, by vasoconstriction. It can save some of the heat it is losing externally and this may be applied internally to the task of warming the water. But in the main the body has only one protection

against the cold mass in the stomach. It must produce more heat. That this condition is associated with increased adrenal secretion—a secretion which has calorigenic powers, that with this mechanism in action shivering may not be relied upon, and that in the absence of shivering the metabolism is considerably heightened by cold, we have shown by our experiments. They definitely support the testimony and the arguments of Voit and Rubner, and offer an explanation of the chemical regulatory device which they postulated.

Evidence recently reported by Hunt and Bright (1926) has shown that adrenalin increases metabolism by action on both the viscera and skeletal muscles. The effect of curare in lowering or abolishing the ability of the organism to maintain its temperature has been used as proof that the chemical agencies for heat production reside in muscles and are subject to the direct nervous control which makes muscles contract. This effect of curare, however, should not be regarded as evidence against the calorigenic service of increased medulliadrenal secretion. Seven years ago, when it seemed possible that a rise of blood pressure from constriction of a denervated splanchnic area could be used to demonstrate reflex adrenal secretion, curare was given by one of us to eliminate disturbing muscular movements. It was soon apparent that the amount of curare that blocked nerve impulses to skeletal muscles greatly reduced the responses from the adrenal medulla. Stewart and Rogoff (1919) have noted effects leading to the same conclusion. Curare would tend, therefore, to stop acceleration of metabolism whether due to increased output of adrenin or to muscular contraction.

In connection with the two modes of meeting a heat deficit—by augmented discharge from the adrenal medulla and by shivering—it is interesting to note the manner in which the organism meets the critical situation presented by hypoglycemia. Cannon, McIver and Bliss (1924) have called attention to two lines of defense which arise when dangerous hypoglycemia is threatening; first, an excitation of the sympathetic system, with attendant larger medulliadrenal secretion, which calls forth sugar from the liver, and second, a convulsive attack, or series of such attacks, in which the sympathetic discharges reach an acme. From the facts presented above it would appear that likewise when there is danger of a lower body temperature from heat loss, a first defense is set up by bringing into action the sympathetic system. Hairs or feathers are lifted till a thicker layer of poorly conducting air is enclosed about the body, peripheral blood vessels are constricted so that the escape of heat by radiation and conduction is diminished, easily combustible sugar is liberated into the blood stream, and adrenin which accelerates combustion is put forth in greater amount. Again, if this first line of defense fails, and the temperature tends to drop in spite of it, there is a second line in

the control of muscular action by the nervous system—shivering is evoked. And just as the convulsive seizures in hypoglycemia are accompanied by a greater discharge of adrenin, so likewise is shivering due to cold (see p. 473). In both circumstances introduction of the muscular factors marks a climax of the action of the automatic arrangements for defense.

It seems probable that the chemical mechanisms for heat production rarely come into service in the ordinary comfortable existence of civilized man. Persons who live through a winter in houses and public buildings, often kept unpleasantly warm, are subjected to few of the exigencies which their ancestors had to meet under primitive conditions. Even if a superficial feeling of being cold signals a possible danger of heat loss, warm clothing is at hand to protect against an amount of heat loss that would call the mechanisms into action. And furthermore, as a rule, the heat produced as a by-product of ordinary functioning of muscles and glands, when associated with quick voluntary protection against heat loss, would be adequate for the ordinary demands of cold weather as most of us have to meet them. If the artificial protection is lacking, however, or if it proves unequal to the occasion, the heat-producing mechanisms are ready, and can be brought into service promptly to help in the emergency.

SUMMARY

To indicate increased secretion of adrenin the completely denervated heart was employed. Since the thyroid gland and the liver were likewise denervated, the adrenal medulla alone was left as a factor capable of causing, humorally, a faster heart beat. The animals thus prepared lived normally in the laboratory.

The first test applied was exposure of the animals to a cold environment. Under these conditions, with no emotional element or struggle involved, the rate of the denervated heart increased between 18 and 33 per cent. After the right adrenal gland was removed and the left was wholly denervated, the same test on the same animals caused the heart rate to decrease (see fig. 1).

The second test was the establishment of a heat debt by introducing a known amount of cold water (between 0° and 1°) into the stomach—a method which is easily available at any time and, with fairly uniform environmental temperature, is satisfactorily quantitative (see p. 471). The heat debt established in cats varied between approximately 1500 and 2000 small calories per kilo (see table 1). There was an initial disturbance of the heart rate due to giving the water, but after that subsided to a plateau, the elevation of rate ranged between 23 and 28 per cent. This increased heart rate may continue for an hour or more (see table 1, fig. 3 *B* and fig. 4). When equal amounts of warm water (between 31° and 34°) were given, the increased rate disappeared in fifteen minutes

or less (see table 1 and fig. 3 *C*). After the adrenal glands had been rendered inactive the test with cold water on the same animals caused only slight acceleration and in some instances depression of the heart rate (see table 1, fig. 3 *D* and fig. 4).

From these observations the conclusion is justified that conditions which would naturally cause a lowering of body temperature induce an increased discharge of adrenin into the circulating blood.

The evidence that secreted adrenin has a calorogenic action is reviewed and two types of experiment are proposed to demonstrate its service to the organism—*a*, its relation to shivering, and *b*, its effect on metabolism in the absence of shivering.

When the heat debt is large (1000 small calories per kilo or more, with the water at 1°) and the room temperature is about 20° it is commonly met by two calorogenic agencies—increased output of adrenin and shivering. Although shivering coincides with the period of greatest medullary discharge (see fig. 1), it is not a necessary condition for the discharge—it may be wholly absent though the heart rate is well accelerated (e.g., no. 26, March 16, table 1).

If in an environmental temperature of about 20° a heat debt of only 900 calories is to be paid, shivering rarely occurs; and if it occurs, it is of short duration (3 minutes). If now the adrenal glands are put out of function, and a heat debt of 900 calories is established, shivering almost uniformly occurs and may last for as long as 17 minutes (see table 2). Thus when the heat-producing service of the adrenal medulla is lacking, the shivering mechanism is resorted to.

Establishing a heat debt averaging 449 small calories per kilo caused in twenty-two observations on eleven human subjects, an average maximal increase of metabolism of 16.4 per cent, with variations ranging upward as high as 38 per cent. These increases were not accompanied by shivering. The development of the peak of the metabolic rate averaged twenty-three minutes after the cold water was taken, and therefore was not due to the disturbance of taking the water. When an equivalent amount of warm water was taken the average increase of metabolism was only 3.1 per cent, and since the time of maximal increase occurred regularly in the first seven minutes of the experiment, it must have resulted chiefly from the disturbance of taking the water (see tables 3 and 4 and also figs. 5 and 6).

In one of our cases regularly and in others occasionally the heat debt induced a preliminary fall of metabolism which was followed by a rise often to a level well above that of the preliminary basal period (see table 5).

When shivering occurs it usually causes a marked and sudden increase of the metabolic rate, which may be as much as 60 or 90 per cent above the basal (see table 6 and fig. 6).

In cold surroundings a given heat debt causes a much greater increase of metabolism than in warm surroundings (see table 7). Our experiments have shown that the same conditions which increase adrenal secretion in lower animals increase metabolism in man, and this without shivering. We conclude, therefore, that a disturbing heat loss evokes activity of the adrenal medulla and that the extra output of adrenin by hastening combustion, serves to protect the organism against cooling.

The experiments of Voit and Rubner and of their opponents are discussed in the light of our experiments. Our experiments obviously have an important bearing on the long-waged controversy over the question of true chemical augmentation of metabolism. They support the contentions of Voit and Rubner that such a process exists in the body and they account for the mode of action of that process.

The effects of curare are considered, and also the rôle of medulliadrenal secretion and of shivering as primary and as secondary defences of the organism against a fall of body temperature.

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